

DIP #604

USMLE Step 2/3 Rapid Review Series 123

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- **Dr Mohammed Zaki**

<https://chat.whatsapp.com/L6dShASc3f97cwHZgCD6Xo>

Welcome. My name is Divine. This is episode 604 of the Divine Intervention podcasts, and in today's podcast, we're going to be continuing the USMLE Step 2 CK and Step 3 Rapid Review series.

This is going to be **series 123**. I'm really going to be going over a lot of material that's actually **really high-yield** to know for the **USMLE exams**.

So let's begin.

Drug-Induced Agranulocytosis & Chloramphenicol Toxicity

What if they give you a question about an individual that just returned to the US from military—like some kind of military deployment?

- This was like, the person just returned like **3 days ago**.
- This person for the past **48 hours** has been having **fevers** and **shortness of breath**.
- The person has been having a **non-productive cough**.
- They tell you that the person is brought to the **emergency room** and they give you some labs.

You notice that:

- The person's **hemoglobin is like 4** and they give you the **hematocrit** of like 12.
- Because remember, your **hematocrit** is 3x your hemoglobin.
- The person's **white count is like 500** or something extremely low.
- The **platelet count** is like 3000, something extremely low.
- Vital signs: person's **temperature is like 101°F**, **hypotensive**, **tachycardic**, **tachypneic**.
- Relevant history: they tell you that this person had an **infection or brain infection** while they were deployed in some **African country** and they received **antibiotic therapy** for that brain infection that they recovered from.

Then they ask you, what is the most likely diagnosis?

- Our friends at the NBME, I can almost promise you that one of the answer choices is going to be **malaria**.
- They're going to put **drug toxicity** as an answer.
- They can throw in something like—what's the thing from **New England** that starts with a B that can also cause **hemolysis**? **Babesiosis**.
- Remember, it's also carried by the **Ixodes tick**.
- They can put some kind of **malignancy** as an answer

So of all these different options I've mentioned, which one should you pick?

- I would really hope you're saying, "Divine, I think the right answer is **drug toxicity**."
- Why is that?

Before I talk about why drug toxicity is the answer, let's talk about why the other answers are wrong.

Why the other answers are wrong:

1. Malaria:

- Can malaria cause **fever**? Yeah.
- Is this person a returning traveller? Yeah.
- Does this person have **anemia**? Yeah.
- But does **malaria** infection (Plasmodium species) cause **pancytopenia**? It **does not**.
- It doesn't cause you to have **leukopenia**.
- It doesn't cause you to have a **thrombocytopenia**—well, you may have thrombocytopenia sometimes.
- But there are just certain facts of the case that are not really well explained, right?
- I just told you that he has a **fever**.
- I don't tell you anything about **tertian fevers** or **quartan fevers**.
- I literally say **nothing** about any of those things.

So, there's no reason you should jump to the conclusion that this person has malaria.

- But if I were NBME—and that's what they totally do to you—then that's a very reasonable answer to put on an exam.

2. Babesiosis:

- Remember, it affects **red blood cells**, so it can cause a person's red blood cells to **explode** and cause **anemia**.
- But again, **Babesia microti** does not really explain the person having **thrombocytopenia** or **leukopenia**.
- By the way, remember, people that have malaria and Babesia can have **jaundice**, they can have **unconjugated hyperbilirubinemia** because of the **hemolysis** those bugs cause.

Babesia is carried by:

- The **Ixodes tick**.
- The **Ixodes tick** carries:
 - **Borrelia burgdorferi**
 - **Anaplasma**
 - **Babesia microti**

3. Malignancy:

- This is **not a malignancy**.
- It just doesn't make sense.
- With malignancy, they will give you a little bit more than just pancytopenia—they've got to give you some **clues**.

Correct Diagnosis: Drug Toxicity (Chloramphenicol)

- This person took **chloramphenicol**.
- **Chloramphenicol** is an **antibiotic**.
- It may not be used in the US much anymore, but it's used in foreign countries.
- I certainly remember chloramphenicol being used quite frequently where I'm from.
- I may or may not have been on **chloramphenicol** at some point in my life.

Key fact:

- Chloramphenicol can cause **agranulocytosis**.
- It can cause **bone marrow suppression**.
- That's why this person basically has **febrile neutropenia** from the **drug**.

Watch out for chloramphenicol.

- Many people think that it can never be tested anymore—that couldn't be further from the truth.
- They may not test it in a person that's from the US, but they'll bring it in with **returning servicemen** or **missionary** questions.

The USMLE has had an enhanced focus on:

- **Returning servicemen and women** over the past 2–3 years.

Other Drugs That Cause Agranulocytosis

- **PTU, methimazole** (anti-thyroid drugs)
- **Clozapine** (antipsychotic)
- **Carbamazepine** (antiepileptic)

USMLE Strategy Insight

- There's an enhanced focus on **basic sciences** in Step 2 and Step 3 now, since Step 1 became pass/fail.
- They test basic science concepts by **rewording** questions.

Example:

- Instead of drug names, they may give you **mechanisms of action**:
 - **Thyroid peroxidase inhibitor** = PTU/methimazole
 - **D2 receptor antagonist** = Clozapine
 - **Anti-epileptic** = Carbamazepine
 - **Ribosomal subunit inhibitor** = Chloramphenicol (50S)

- They will probably not put **50S**, because they know that if they put **50S**, it kind of triggers people's memories—some neurons start firing from previous **USMLE exams**.
- So you may not see that on your exams.
- They can just put **ribosomal subunit inhibitor** or something like that.

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- Right. So again, that's the concept of a **derivative**, right.
 - You've heard me talk about **derivatives** so much, so much, so much, so much, right.

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- Basically, the **USMLE** takes what you know and just **translates it to a different language**.
 - Right, like hey, how can we confuse Divine?
 - Well, Divine's first language is English.
 - But hey, just speak a language that Divine does not understand.
 - Right, maybe, I don't know—start speaking like some language Divine doesn't understand.
 - If you speak that language Divine doesn't understand, Divine just gets really, really confused fast, right.

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- So that's the same thing with the **USMLEs**.
 - That's why people say, “Oh, the exam was so **weird and crazy** and whatnot.”
 - No, it's not that the exam was weird or crazy or whatnot—they just put it in a **language that you are not used to**.

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- It's the **same concepts**.
 - They are still largely testing from year to year, although there is a lot of **changes** they've made over the last, like I'll say **11 months** or thereabouts, right, with **Step 2 and Step 3**.
 - But I will say that they just put things in a **different language**.

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- So, how can you make an **agranulocytosis question** harder than it needs to be?
 - Just change the wording of the answers.
 - Instead of putting the **drug names**, just put the **mechanisms of action**.
 - That's a way to make it a **second-order** or **third-order** question.
 - It's a simple question, but just make it a little harder by stretching your thinking a little bit.

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- So just keep that at the **back of your mind**.
 - And remember, **chloramphenicol** is used largely for **meningitis**.
 - It's used largely for **meningitis** in **foreign countries**.
 - It's very, very effective for the management of **meningitis**.
 - And again, it's a **50S inhibitor**.
 - Although, remember, sometimes you can use **chloramphenicol** for **Rocky Mountain spotted fever**.
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- But really on the **USMLE**, most times if you want to treat that infection caused by **Rickettsia rickettsii**, you're going to be using a **tetracycline**, right.
 - And how do **tetracyclines** work?
 - Do you remember?
 - It's a **30S inhibitor**.
 - It's not a **50S inhibitor**.
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- So again, if they want to make this question harder:
 - They can talk about like a **brain infection** from a **foreign country**, and then they put **30S inhibitor** as an answer.
 - They put **50S inhibitor** as an answer.
 - Don't pick the **30S inhibitor**.
 - Pick the **50S inhibitor**, right.
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- I would really hope that you're not using a **tetracycline** to treat **meningitis**, right.
- I would hope you're using—if you have to pick between **tetracycline** and **chloramphenicol** for **meningitis**, it would make more sense to use **chloramphenicol** for **meningitis**.

Hereditary Spherocytosis & Osmotic Fragility

- So what if they give you a question about an **individual**, and they tell you that this person—they make it like a question involving an **experiment**.
 - They tell you that this person has a **long history of anemia**, has required **multiple blood transfusions**.
 - You notice that the person's **total bilirubin is elevated** and their **unconjugated bilirubin is elevated as well**.
 - And you also notice that this person's **lactate dehydrogenase is pretty elevated**.
 - And then they tell you that some **blood samples were taken from the patient** and they were placed in **hypotonic solution**, and they noticed an **increased release of hemoglobin** from many of the patient's blood samples compared to controls.
 - And then they ask:
 - Which of the following is the **most likely underlying pathophysiology**?
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- I really hope you're picking an answer that talks about **red blood cell membrane defect**.
 - Or they can even ask a question:
 - "Which of the following modes of inheritance is most associated with the patient's presentation?"
 - And you want to pick the answer that says **autosomal dominant**, right.
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- So hopefully you've kind of gotten at this point that I'm talking about here: **hereditary spherocytosis**.
 - Now I know some of you are like,
 - "Divine, but you didn't say anything about the person being **European**."
 - You didn't say anything about the person having increased **MCHC**—increased **mean corpuscular hemoglobin concentration**.
 - You didn't say anything about **spectrin** or **ankyrin** in the question.
 - How did you expect us to answer this question?"
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- So let's talk about it, right.
 - Again, this is something that our friends at the **NBME** love to do these days.
 - I know you may be like,
 - "Divine, what are you saying about taking a person's blood samples and putting it in hypotonic solution and then seeing more hemolysis compared to controls?"

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- They're basically describing the **osmotic fragility test**.
 - They won't come out and use the words **osmotic fragility test**, but they will give you a **derivative**, or they will **describe it**.
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- Because if you really think about it, that's a very easy way to test that a person's **red blood cell is very concentrated**.
 - Because remember, if something is concentrated and you expose it to a **hypotonic solution**, fluid is going to rush into that thing and make it **swell and explode**.
 - So that's why this person's blood samples had **more hemolysis compared to controls**.
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- So they can basically make like a **weird experiment-style question**.
 - Like, I'm not saying an experimental question, but you describe an experiment in a question just to test your knowledge of **osmotic fragility test**, right.
 - Again, this is something I'm sure you've heard of.
 - This thing I'm saying is **not new information**, but again, just written in a **somewhat different way**, right.
 - So again, you want to get used to these kinds of thoughts on your exam.
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- So let's talk about **many of these other labs** and what they mean.
 - So this person — again — they have **hereditary spherocytosis**, which as we know is an **autosomal dominant disorder**.
 - And it involves **mutations in proteins** like **spectrin** and **ankyrin**.
 - **Band proteins**.
 - basically, those things are **red blood cell membrane defects**.
 - So this is **not a hemoglobin problem**.
 - It's a **hemoglobin container problem** — it's a **red blood cell membrane problem**.
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- So when you have these **red blood cell membrane defects**, the thing that's unfortunately going to happen is that your red blood cells are going to be very **concentrated**.
- Remember, what is **concentration**?
 - Concentration is **mass per unit volume**.
 - It's like literally **mass/volume**.
 - So the **mass of hemoglobin is totally fine**, but the **volume** that you've placed it in is very constrained — is very small.

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- It's almost like you don't have enough **membrane** to go around.
 - So in those circumstances, what's going to happen?
 - In those circumstances, the thing that's going to happen is that the cell is going to be **super concentrated**.
 - So if you put it in **hypotonic solution**, it's going to **explode**.
 - That's literally the basis of the **osmotic fragility test** that we use for **hereditary spherocytosis**.
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- Although one other test you may see on your exams is the **eosin-5-maleimide assay** — the **eosin-5-maleimide dye assay**.
 - That's probably a more modern way to test for **hereditary spherocytosis**.
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- And again, why did this person have the **jaundice** and **unconjugated hyperbilirubinemia**?
 - Again, it's because of **hemolysis**.
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- When a red blood cell **hemolyzes**, you have these enzymes like **heme oxygenase** and **biliverdin reductase** — they do all those fancy things.
 - Don't worry, this is not a **Step 1 podcast**.
 - I'm not going to go into all of that.
 - But then you make **unconjugated bilirubin**.
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- The thing is, it's not like you have some kind of **enzyme defect**.
 - It's not like you have a **UDP-glucuronyltransferase defect**, like we see in **Gilbert syndrome** or **Crigler-Najjar**.
 - The problem is that you're just making **so much unconjugated bilirubin** that you're **overwhelming** the ability of **UDP-glucuronyltransferase** to deal with it.
 - So that's why those people have those problems.
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- And honestly, you may notice that many times, **hereditary spherocytosis** — they can give it as a **jaundice question** even in a **newborn**, for example, or a **jaundice question in a little child**.
- Because remember, as little kids, you don't have a ton of **UDP-GT activity**.

- Actually, this is a **little-known fact** among many medical students or people taking the **USMLE**:
 - When you are born, you actually have only about **1% UDP-GT activity** compared to an adult.
 - That's one of the reasons — I promise I'm going to go back to **hereditary spherocytosis** because there's one or two things I want to say there —
 - But that's one of the reasons why **newborns are predisposed to jaundice**.
- You may wonder, why is it that **newborns are predisposed to jaundice**?

Many factors:

- Number one is they have **very little activity** of the enzyme that conjugates **bilirubin**.
- Number two is that **in utero**, they don't really use their lungs.
 - When you're in utero, you're not using your lungs.
 - Your lungs are basically a **bag of fluid** in utero.
 - So that is interpreted by the fetus as a state of **relative hypoxia**.
- So in utero, you may actually — you actually make **tons of erythropoietin**.
- That drives **polycythemia**, right.
- And also, what may be another cause of **hypoxia in utero**?
- Well, think about the kind of **hemoglobin** you're working with in utero.
- You're working with **hemoglobin F**.
- **Hemoglobin F** is $\alpha_2\gamma_2$, right.
- That **γ -subunit** is **not very willing to release oxygen to tissues** — it just isn't.
- So because it's not very willing to release oxygen to tissues, there's like some **mild, low-level tissue hypoxia** that goes on in utero.
- Remember, there is a reason why after you're born, you switch from **hemoglobin F** to **hemoglobin A**.
- **Hemoglobin A** is $\alpha_2\beta_2$.
- That **β -subunit** has a **lower affinity for oxygen** compared to the **γ -subunit**.
- The **β -subunit** is **more willing to release oxygen to tissues**.
- So that's one of the reasons why after you're born, it's like,
 - “Gee, all these red blood cells you made while you were in utero — I don't really need them anymore.
 - I have like legit hemoglobin now — I have **hemoglobin A**.”
- So you start **breaking down** all those red cells.
- You're breaking down all these **excess red cells** you made in utero.

- And you **don't have enough enzyme** to help you **conjugate that unconjugated bilirubin**.
 - That's going to put you in trouble.
 - Most kids don't have that problem, but some kids **really can't handle it**.
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- So you can already begin to see why they can give you a **jaundice question** in a **neonate** or whatever — in a child that has something like **hereditary spherocytosis**.
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- And then the last thing I want to discuss is:
 - Why is the **lactate dehydrogenase** high in **hereditary spherocytosis**?
 - Well, LDH is high because **LDH is an intracellular enzyme**.
 - **LDH** stands for **lactate dehydrogenase**.
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- If you remember from **Step 1 biochemistry**, basically the end of **glycolysis** is with **pyruvate**.
 - **Pyruvate** is converted to **lactate** via **lactate dehydrogenase**, right.
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- And **lactate dehydrogenase** is **heavily expressed in red cells**, because remember — red cells don't really have the ability to do **oxidative phosphorylation** like we see in many other cells of the body.
 - So because they don't have that ability, they're not particularly good — I mean, they run a lot of **glycolysis**.
 - **Glycolysis** is the **primary energy source** for a red blood cell.
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- There are other sources, sure — but **glycolysis is the primary energy source**.
 - So they run **LDH**, they use **LDH** probably a lot more than other cells.
 - So if a lot of red cells are **exploding**, it would make sense that you should see a lot of **LDH in the circulation**.
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- Although, remember — any time you have a lot of **inflammation** or a lot of cells kind of **breaking down**, like:
 - Let's say you're being treated for **leukemia** or **lymphoma** — or even not being treated, even if you just have those things —
 - Because those cells are like **fast-die-young cells**, they don't live very long — that can raise your **LDH**.

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- And then another classic cause of elevated **LDH** on the **USMLE** are things like **transfusion reactions**, or a person having **sarcoidosis**, for example.
 - Because remember, **sarcoidosis** is kind of like an **inflammatory state**.
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- Again, all these things I'm talking about that are kind of **basic science**, that you think are not important —
- I promise you, they are **very, very important** for your exams.
- I'm not talking about them because I just like to hear myself speak.

B12 Deficiency in Crohn's Disease

- Alright, now next I want to talk about—
- So what if they give you a question about a **patient**, and they tell you that for the past like **2 months**, this person has been having **shortness of breath**.
- That with minimal activity, the person just feels very **short of breath**.

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- And they tell you that this person has a past history of **Crohn's disease**.
 - He has a long history of **Crohn's disease**, and the person has **not seen a physician** over the last like **3 years**.
 - And then they give you, like a—
 - They give you a **blood smear**, and they show you like this **neutrophil** that has like a bunch of **rounds inside it**.

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- A lot—like a **lot of nuclei**, right.
 - Like **lots and lots and lots and lots of nuclei** or **nuclear lobes**, or whatever.
 - And then they ask you:
 - Which of the following is the **most likely cause** of this patient's presenting symptoms?

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- And they give you a **hemoglobin** of like **8** or something little like that.
 - And then they give you an **MCV**, right—although to be honest with you,
 - I can almost promise you they probably will **not give you an MCV**, because that will make the question a little too **easy**.

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- So and then they ask you about the **underlying mechanism**, right.
 - And then they can put an answer that says **dietary deficiency**.
 - They can put an answer that says **decreased sunlight exposure**.
 - They can put an answer that says **malabsorption**.
 - They can put an answer that says—let's see Divine, what else can we think about—
 - They can put an answer that says **autoimmune disease**.
 - They can put an answer that says **drug toxicity**.
 - Or they can put an answer that says **bone marrow failure**, right.

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- So I love these things.
 - In fact, I'm going to be doing this more and more—kind of giving like, what I think is a very effective method with these **rapid reviews**:
 - Just give a **bunch of possible answers** and discuss why those possible answers will be **right** or **wrong**.
 - And just discuss some **USMLE gamesmanship**, so you're not just learning **content**, but you're learning **how to take tests**.

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- So, for example, right—this person has **Crohn's disease**.
 - And you see this **white blood cell**, this **neutrophil**, that has **lots of nuclei** in the cell.
 - That's a **hypersegmented neutrophil**, obviously.
 - And the cause for this person is going to be a **B12 deficiency**.
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- So that's why you notice I put on a lot of **B12-related answers**, just to see if you can really pick up on the right one.
 - And let's talk about the **wrong answers first**, and why they would be **wrong**.
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Dietary Deficiency:

- That would be **wrong**.
 - This person does **not** have a **dietary deficiency of B12**.
 - We're not told that they're like **vegans**, for example.
 - So I would not jump to that.
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Autoimmune Phenomenon:

- I would not pick **autoimmune phenomenon**, because I would think of autoimmune phenomenon more likely when they give me another **history of an autoimmune disease**,
 - Like **Hashimoto's**, or **Sjogren's**, or something like that.
 - Because I've just kind of seen this many times with the **USMLEs**:
 - When they are testing an **autoimmune disease**—not always, but many times—they will give you a past medical history of **another autoimmune disease**.
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Drug Toxicity:

- This is not **drug toxicity**, right.
 - There are not many drugs, honestly, that cause a **B12 deficiency**.
 - The only thing I can think of, like **bug-wise**, not a **drug**, but a **bug** that can cause **B12 deficiency**, I believe, is the **fish tapeworm—Diphyllobothrium latum**.
 - That can infect your **terminal ileum** and cause problems.
 - And it also loves to just kind of throw on **B12**—I guess **B12** is its **snack of choice**.
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Bone Marrow Failure:

- I would not pick **bone marrow failure**, because if you have **bone marrow failure**, you will **not only** have **anemia**.
 - You will also have a **pancytopenia**—your **platelet count** should be **low**, and your **white blood cell count** should be **low** as well.
 - We don't see that.
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Correct Answer: Malabsorption

- So the answer here is **malabsorption**.
- So how does **malabsorption** factor into all I've just stated?
- Well, **malabsorption** factors in because remember that **Crohn's disease**—
 - One of the areas it touches is the **terminal ileum**.
 - The **terminal ileum** is probably the most commonly involved area of the **GI tract** in **Crohn's disease**.

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- So remember, **B12 is reabsorbed in your terminal ileum**.
 - And we have, like, **years' worth of B12** in the body.
 - But again, if you have **poorly controlled Crohn's** and you don't want to see your doctor for a while,
 - You're probably not on the right medications.
 - You're getting a ton of **inflammation** that's going to mess up your **terminal ileum**.
 - And that's going to cause **B12 deficiency**.

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- So that's something that's pretty **high-yield** for your exams.
 - That's how this person got **B12 deficiency** and has these **hypersegmented neutrophils**.

Biochemical Clues:

- And remember, when you have **B12 deficiency**, your **methylmalonic acid levels** are going to be **high**.
- And your **homocysteine levels** are going to be **high**.
- That's clearly different from **folate deficiency**, where your **methylmalonic acid levels will be normal**, but your **homocysteine levels will be high**.

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- So I know today we may have just talked about **three vignettes**, but it's kind of intentional.
 - Think of what we discussed today as falling under the purview of **multi-system processes and disorders** on the **USMLEs**.

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- They love **hematology** many times for **multi-system processes and disorders** because there are just so many **wonderful integrations** you can make with that stuff, right.
 - So I would certainly encourage you to know that.
 - Like if you notice, even just one vignette, we kind of spend like **eight to nine minutes** discussing it, right.